REMARKS

The undersigned would like to thank the examiner for time taken to previously discuss via telephone the outstanding rejections in the application.

Claims 97 and 157 through 176 are pending in the application. Claims 176 has been withdrawn from consideration, and claims 97 and 157 through 175 are under examination.

Pervious rejections set out in an Office Action dated April 2, 2007 were withdrawn in view of amendments made in a response filed July 2, 2007. Applicant's remarks made in the July 2, 2007 amendment were discussed in the instant office action As they apply to new grounds of rejection.

Claim 97 is amended to recite that individual microchips have different oligonucleotide sequences attach at different locations as supporting the specification at, for example, page 17, lines 11-13, describing the precise placement of probes in an array of 64 rows by 64 columns; Figure 2A and 2B, described at page 19, lines 1-14, illustrating arrays of oligonucleotides on microchips and the microchips themselves arrayed on a support; and Example 1, which describes methods for precisely positioning specific oligonucleotides at specific locations. The amendment therefore include no new matter.

The objection to the claims

Claims 176 was objected to for being identified as "previously presented" when the claim has been withdrawn. The claim identifier has been corrected herein.

The section 112, first paragraph, written description rejection

Claims 97 and 157 through 175 were rejected under 35 USC §112, first paragraph for assertedly lacking written descriptive support in the specification. Specifically, the examiner asserted that passages in the specification on which the applicant relied for previous amendment to claims 97 and 166, wherein the term "physical barriers" was added to the claims, "teach physical separation and hydrophobic and groove barriers, the hydrophobic and groove barriers being species of physical barriers" The examiner then added, "...neither

the cited passages nor the entire specification defines what is encompassed by the generic physical barrier as recited in Claims 97 and 166." [Office Action at the paragraph bridging pages 3 and 4] Thus, the examiner concluded that the specification does not support the invention as claimed. The applicant respectfully disagrees.

As the examiner noted below, and the specification teaches at pages 40 through 42, hydrophobic grid membrane filters (HGMFs) were known as early as 1989 and demonstrated for use with analytical food microbiology in the disclosure of Peterkin, et al. (specifically at page 40 of the instant specification), a reference relied on by the examiner in combination with the disclosure of Southern et al., for rejection of claims as discussed below. The specification also teaches at page 41 that Sharp, et al., also in 1989, published on the use of a commercially available ISO-GRID HGMF for maintaining microbial culture, and that Peterkin et al., further published on improved cellular DNA binding on specifically treated HGMFs. The disclosure makes expressly clear (for example at page 41, lines 31 through 34) that all of these HGMF uses accomplished an objective different from the materials and methods for nucleic acid sequence analysis by oligonucleotide hybridization and ligation disclosed and claimed in the instant application..

This point is made clear in the instant specification at page 42, lines 7 though 19,

> Two basic problems have to be solved. Manipulation with small (2-3 mm) chips, and **parallel execution of thousands of the reactions**. The solution of the invention is to **keep the chips and the probes in the corresponding arrays**. In one example, chips containing 250,000 9-mers are synthesized on a silicon wafer in the form of 8x8 mM plates (15 μM/oligonucleotide, Pease et al., 1994) arrayed in 8x12 format (96 chips) with a 1 mM groove in between. Probes are added either by multichannel pipet or pin array, **one probe on one chip**. To score all 4000 6-mers, 42 chip arrays have to be used, either using different ones, or by reusing one set of chip arrays several times.

To accomplish this end, the arrays of the invention, and hybridization reactions carried out on the individual microchips, are maintained in separate regions on the single support or as an array of chips for efficient simultaneous use (not chips that are independently used in time or handled independently) as described in the description of Fig. 2, using physical barriers or hydrophobic strips. In one aspect, the physical barrier is taught to be a groove as discussed in the disclosure cited immediately above, and Example III, also as discussed above, teaches the use of hydrophobic materials known in the art. Against this teaching, the worker of ordinary

skill in the art would readily envision any of a number of alternative means for maintaining separation of individual hybridization reactions through use of commonly known and routinely utilized in non-analogous arts.

Thus, in view of the intended use and the exemplified use of materials known in the art, it is evident that the present invention incorporates materials which need not be described in further detail to understand that the inventor was actually in possession of the invention exactly as claimed at the time the application as filed. Indeed, "[a] patent need not teach, and preferably omits, what is well known in the art." *Faulkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)). Accordingly, the applicant submits that the specification fully describes the invention and the rejection must be withdrawn.

The rejection under 35 USC §102(a)

The examiner rejected claims 97, 159-160, 166, and 169-170 under 35 USC §102(a) for being directed to subject matter assertedly anticipated by the disclosure of Datta, et al., Applied and Environmental Microbiology Jan 1993, 59:144-149 [hereinafter "Datta"]. The examiner addressed independent claims 97 and 166 alleging that Datta discloses a support comprising an array of microchips, referring to Figure 1, wherein the microchips each comprise different oligonucleotide probes immobilized on the surface and separated by a physical barrier. In this instance the examiner asserted the barrier to be space, and referred to page 145, right column, and page 146, Figure 1. The applicant respectfully disagrees.

In the passages referred to by the examiner, Datta describes at page 145 preparation of nitrocellulose and nylon filters for dot blot hybridization (first paragraph in the section entitled "Preparation of membranes for hybridization"). Use of the blotted membranes is described in the paragraph bridging pages 145 and 146, and the results from subsequent autoradiography of the individual membranes after hybridization are shown in Figure 1. Figure 1 is a side-by-side comparison of radioactivity detected (autoradiograms) from two separate filters that were hybridized in separate hybridization with two distinct probes. (See Legend of Figure 1.)

Claim 97 requires **a support on which microchips are arrayed, i.e., "a support comprising an array of microchips,"** each microchip having an array of oligonucleotides thereon. In their arrayed positions, each microchip is separated from each other microchip, but still on the support, positioned in such a way so as to allow separate hybridization reactions to be carried out with each microchip and to preclude probe hybridization solutions used with one microchip to bleed over to any other microchip which is used in parallel in a separate hybridization reaction with a different probe. Stated another way, the arrayed miniaturized chips ('microchips") are used together at the same time by virtue of being arrayed (e.g. placed and secured in specific grid locations) on a single support. See, for example, page 42 of the specification, lines 7-11,

> Two basic problems have to be solved. Manipulation with small (2-3 mm) chip, and parallel execution of thousands of the reactions. The solution of the invention is to keep the chips and the probes in the corresponding arrays.

Comparing the Datta disclosure to the subject matter in claim 97, nothing in Datta discloses or suggests that membrane preparation or hybridization protocols were carried out under miniaturized-scale conditions, i.e., Datta does not even suggest that the membranes could be considered miniaturized in size. The applicant must therefore presume that the examiner is of the opinion that an individual "dot" of DNA immobilized on the dot blot membrane is analogous to a microchip. This presumption, however, cannot be supported by the facts.

In claim 97, each microchip on the support is recited to have an array of oligonucleotide attached. Arraying oligonucleotides to form a microchip is distinct from spotting a membrane to produce a single dot on a dot blot. See in the instant specification, for example, at page 17, lines 11-13, describing the precise placement of probes in an array of 64 rows by 64 columns; Figure 2A and 2B, described at page 19, lines 1-14, illustrating arrays of oligonucleotides on microchips and the microchips themselves arrayed on a support; and Example 1, which describes methods for precisely positioning specific oligonucleotides at specific locations on a support. Even if one were to incorrectly postulate that the membrane filters used in Datta's dot blot are analogous to microchips, nothing in Datta teaches or suggests that the spotted membranes were subsequently positioned (i.e., arrayed) *on a single support*. The absence of a single support onto which the membranes are array is evidenced by the examiner's reliance on some undefined "space" as being a physical barrier

as recited in the claims. In Datta, the last paragraph on page 145 states that the filters were hybridized in buffer, so the "space" to which the examiner refers *must* be the free floating nature of the filters in the buffer solution, *i.e.*, there is no connection between any two filters while in solution. "Space" as a barrier therefore implies a disconnection which the support recited in claim 67 provides; even though individual microchips are physically separated, they remain connected by virtue of each being arrayed on the single support. Thus, Datta dose not disclose the subject matter of claim 97.

The same analysis hold for the subject matter of claim 166 which also requires a support (as in claim 97) comprising multiple arrays of immobilized oligonucleotides (as in claim 97) wherein each array is separated by a physical barrier or a hydrophobic surface from every other array (also as in claim 97) and each array having oligonucleotides with different sequences attached thereto. Since it is shown above that Datta does not disclose a support of any kind having a multiplicity of arrays associated therewith, Datta cannot disclose the subject matter of claim 166.

Because Datta does not disclose each and every reference limitation recited in independent claims 97 and 166, the reference cannot anticipate the recited subject matter and the rejection of these claims must be withdrawn. Moreover, since a dependent claim incorporates each limitation of a claim from which it depends (35 U.S.C. §112, fourth paragraph) the limitations of claims 97 and 166 attach to each of the dependent claims which, as explained above, Datta does not disclose. Accordingly, the rejection of all claims over the disclosure of Datta must be withdrawn.

The rejection under 35 USC §102(e)

The examiner also rejected of claims 97, 157-160, 163-170 and 173-175 under 35 USC §102(e) for being directed to subject matter assertedly anticipated by the disclosure of Winkler, US Patent No. 5677195 [hereinafter "Winkler"]. Specifically addressing claim 97, the examiner asserted that Winkler discloses a support comprising an array of microchips each having an array of oligonucleotide probes immobilized thereon. More specifically, the examiner made reference to a support which assertedly "comprises an array of regions (#1004 [Fig 12]) wherein each region comprises an array (i.e., plurality) of probes immobilized thereof (Column 7, lines 10-41; Column 16, lines 22-53, and Fig 12)." Further, the examiner

asserted that the microchips are separated by physical barriers (referring to Column 22, lines 8-14), the regions have a predominant species of probes (referring to Column 7, lines 31-38, and thus "in other words, the region has an array of probes immobilized thereon as recited in the instant claims." With regard to the rejection of claim 97, the applicant respectfully disagrees.

This rejection is in large part identical to the rejection of claims over the disclosure of Winkler set out in the April 2, 2007 office action. In response to that rejection, the applicant stated at pages 5-6 of the amendment,

> Winkler does not disclose an array of microchips, i.e., an array of arrays. Instead, the disclosure describes "formation of **arrays of large numbers of different polymer sequences**" and **these polymers are attached to the same solid support**. This Winkler product is distinct from the instantly claimed invention, as evidenced by the description of microchips in Example III beginning at page 40.
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> Specifically, Example III describes embodiments wherein 3 mm x 3 mm chips, each chip having 6mer oligonucleotides attached thereto, are arrayed on a 20 cm x 20 cm surface. In another example, 9mer oligonucleotides are attached to 5 mm x 5 mm chips and 4000 units of such chips are used to prepare a 30 cm x 30 cm array. In still other examples, the Example III refers to Figures 2A, 2B and 2C depicting square arrays of 4000 to 16000 oligochips. For each of these arrangements, individual chips are first prepared which are then be arrayed on a support in any desired format.
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> In contrast, the Winkler product consists of a support on which polymers are either directly synthesized or directly attached. **At best, the Winkler product is arguably analogous to a single microchip in the instantly claimed invention**, but still differs from the instant microchips in that Winkler designs the product to have a substantially pure polymer at each discrete location on the support. As Winkler states beginning at col. 7, line 25, it is this substantial purity within a predefined region that distinguishes that region from other predefined regions on the substrate. In both Winkler and the instant invention, a single unit array (i.e., a single microchip in the instant invention) of oligonucleotide spots can be seen as an "array of random molecule arrays" but a unit array is completely different from an array of two or more arrays of oligonucleotide spots, i.e. from an array of two or more "arrays of .random molecule arrays." Thus Winkler does not disclose an array of oligonucleotide spot arrays wherein the oligonucleotide spot arrays within composite array (i.e., the array or arrays, or arrayed microchips) are separated by physical barriers or hydrophobic spaces. [Emphasis added.

In the instant office action, the examiner responded to arguments previously submitted as they apply to the new grounds for rejection, but in response to the applicant's

reply to rejections based on Winkler, the examiner only addressed the issue of a substantially pure polymer at a discrete location on the support. The examiner did not address the contention that the structure disclosed by Winkler is analogous only to a single microchip rather than an array of microchips wherein each microchip has an array of oligonucleotide attached thereto. The applicant explained above that the specification teaches that an array is an ordered positioning of oligos on a microchip and microchips on a support (See, Example III), and not simply a plurality of oligonucleotides as asserted by the examiner. Thus, the applicant repeats and emphasizes that the structure described by Winkler is at best analogous to a single microchip, and not at all analogous to an array of oligonucleotides on microchips arrayed on a single support. Accordingly, Winkler does not disclose the subject matter of claim 97.

With regard to the subject matter of claim 166, the same argument applies. Contrary to the examiner assertion, and as discussed herein and previously, Winkler does not disclose multiple arrays of oligonucleotides on a support because an array as defined in the instant specification is not simply a plurality of oligonucleotides or a region or spot on a support with a randomly attached plurality of oligonucleotide molecules. As discussed above, Winkler at best might arguably be considered a single support comprising an array of oligo, but it cannot be analogized to a multiplicity of arrays. Accordingly, Winkler does not disclose all limitations of the subject matter of claim 166.

Because Winkler cannot anticipate the subject matter of either claim 97 or 166, it cannot anticipate the subject matter of any claims depending from the independent claims and the rejection over the disclosure of Winkler must be withdrawn.

The rejections under 35 USC §103

The examiner also maintained rejection claims 162 and 172 under 35 USC §103 for being directed to subject matter allegedly rendered obvious by the disclosure of Winkler in view of the disclosure of Augenlicht, US Patent No. 4981783 [hereinafter "Augenlicht"]. In addition, the examiner ejected claims 161 and 171 over the disclosure of Winkler in view of the 1988 Stratagene catalog at page 39.

For reasons discussed above, the disclosure of the primary reference Winkler cannot anticipate the subject matter of the broad claims because it fails to disclose each and every limitation of these claims. Because the limitations of the broad claims attach to the subject matter of the dependent claims, Winkler cannot disclosure all limitations of these claims either. Adding in the disclosure of either Augenlicht or the Stratagene catalog fails to correct this deficiency in the Winkler disclosure because neither additional reference discloses arrays of oligonucleotides on physically separate microchips which are themselves arrayed on a support as recited in claim 97, or multiple oligonucleotide arrays which are arrayed on a support and wherein each array is separated with a physical barrier or a hydrophobic surface from every other array as recited in claim 166.

Because the combined disclosures fail to teach each and every limitation of the invention, the combination cannot render obvious the claimed subject matter and the rejections over the disclosures of Winkler and Augenlicht or Stratagene must be withdrawn.

The section 102(b) rejection over Southern

.Claims 97, 158-160, 163-166, 168-170 and 173-175 were rejected under 35 USC §102(b) for being directed to subject matter assertedly anticipated by the disclosure of Southern, Genomics (1992) 13:1008-1017 (hereinafter "Southern") in view of Peterkin et al., Food Microbiology (1989) 6:281-284 (hereinafter Peterkin").

Regarding claims 97 and 158, the examiner asserted that Southern discloses an array of microchips, each having an array of oligonucleotide probes immobilized thereon. Further, Southern is alleged to teach that each array is in one of four quadrants and each array is physically separated "because a quadrant defines a physical location". The examiner admits that Southern does not teach a physical or hydrophobic barrier, but relies on the disclosure of Peterkin to rectify this deficiency. The same rejection is also made for the subject matter of independent claim 166. **This combination of references therefore raises the initial questions as to whether the examiner is making the rejection under section 102 or section 103. The examiner is reminded that the standards for rejections under 102 and 103 are not the same, and by setting out an ambiguous rejection, the applicant is put at a disadvantage not knowing how to fully respond.**

Regardless of a purported statutory basis for the rejection, the applicant submits that the disclosure of Southern in Fig. 3 is an arrangement of four arrays of oligonucleotides, wherein each array is identical in terms of the oligonucleotides which are attached to each array in a way that gives rise to replicate measurements of the same hybridization reaction. In other words, each of the four arrays is a replicate of the other three and each therefore has exactly the same oligonucleotides attached in the same location. (See, the legend to Fig. 3 which states, "The plates carried four copies of an array of all 256 octapurines, one in each quadrant." [Emphasis added.]) In this arrangement, parallel use of individual arrays in the same hybridization reaction is made possible, but parallel use in different hybridization reactions (for example using different labeled probe for hybridization reactions in individual unit arrays on the same single support) cannot be accomplished because the individual arrays described by Southern lack physical or hydrophobic barriers between unit arrays, thereby allowing different hybridization reactions to bleed over onto other arrays. Without barriers as recited in the instant claims, the complete Southern arrangement is reduced to a "single reaction" array, while the products of the instant claims, as discussed in detail above, are "multiple reaction" arrays.

Moreover, using the examiner's logic, the array described in Southern can be arbitrarily divided into any number of sections wherein each section is declared to be a unit array based simply on its physical location. Such an arbitrary division is not possible with the products of claims 97 and 166 wherein a pre-specified number of unit arrays are expressly defined by the recited barrier (and ultimately the distinct reactions allowable by pipetting different solution components such as different labeled probes or different target DNA in the defined areas on the support).

Southern therefore cannot anticipate the subject matter of independent claims 97 and 166 because each and every limitation of the claims is not found in the reference. Likewise, this deficiency in Southern is not rectified with addition of the disclosure of Peterkin, relied on by the examiner only for disclosure of hydrophobic separation components, and as a result, the combination of references cannot render obvious the subject matter of these independent claims. Accordingly, neither a 102 nor a 103 rejection can be sustained based on the disclosure of Southern and the rejection, regardless of its statutory basis, must be withdraw,

The double patenting rejection

The examiner also rejected claim 97, 157 and 175 under the judicially created doctrine of obviousness type double patenting over claims 37 through 76 of US Patent No. 6,401,267 (hereinafter "the '267 patent"). A terminal disclaimer accompanies this paper thereby obviating the rejection.

CONCLUSION

In view of the amendments and remarks made herein, the applicant submits that all claims are in condition for allowance and requests notification of the same.

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Respectfully submitted,

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